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Long Term Outcomes Following Catheter Ablation of Ventricular Tachycardia in Patients with and without Structural Heart Disease

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Short title: Long term outcomes after VT ablation

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Abstract

Background

Long-term outcomes following ventricular tachycardia (VT) ablation are sparsely described.

Objectives

To describe long term prognosis following VT ablation in patients with no structural heart disease (no SHD), ischemic (ICM) and non-ischemic cardiomyopathy (NICM).

Methods

Consecutive patients (n=695; no SHD 98, ICM 358, NICM 239 patients) ablated for sustained VT were followed for a median of 6 years. Acute procedural parameters (complete success [non-inducibility of any VT]) and outcomes after multiple procedures were reported.

Results

Compared with patients with no SHD or NICM, ICM patients were the oldest, had more males, lowest left ventricular ejection fraction (LVEF), highest drug failures, VT storms and number of inducible VTs. Complete procedure success was highest in no SHD, compared ICM and NICM patients (79%, 56%, 60% respectively, P<0.001). At 6 years, ventricular arrhythmia (VA)-free survival was highest in no SHD (77%) than ICM (54%) and NICM (38%, P<0.001) and overall survival was lowest in ICM (48%), followed by NICM (74%) and no SHD patients (100%, P<0.001). Age, LVEF, presence of SHD,

acute procedural success (non-inducibility of any VT), major complications, need for non-radiofrequency ablation modalities, and VA recurrence were independently associated with all cause mortality.

Conclusions

Long term follow up following VT ablation shows excellent prognosis in the absence of SHD, highest VA recurrence and transplantation in NICM and highest mortality in patients with ICM. The extremely low mortality for those without SHD suggests that VT in this population is very rarely an initial presentation of a myopathic process.

Keywords: ventricular tachycardia; catheter ablation; structural heart disease; ischemic cardiomyopathy; non-ischemic cardiomyopathy.

Introduction

Catheter ablation for sustained monomorphic ventricular tachycardia (VT), as an adjunct to medical therapy reduces the morbidity associated recurrent VT.[1] Prior studies on outcomes following VT ablation report a limited duration of follow up, mostly up to 2 years; thus data on long-term recurrence and mortality following VT ablation is limited.[2, 3] Furthermore, whilst substrate differences between ischemic and non-ischemic cardiomyopathy (ICM and NICM respectively) have been appreciated,[4] few studies have directly compared the outcomes of these groups in follow up, or have been underpowered to detect differences in major endpoints such as mortality and transplantation or have lacked a control group of patients without structural heart disease (SHD).[5, 6] In this study, we followed 695 consecutive patients either with no SHD, ICM or NICM for a median of 6 years to directly compare the acute procedural efficacy and long-term prognosis in these groups following catheter ablation of sustained monomorphic VT. We also examined clinical and procedural factors for their ability to predict recurrent ventricular arrhythmia (VA), and mortality following VT ablation.

Methods

This was a retrospective series of 695 consecutive patients who presented for catheter ablation of sustained monomorphic VT between 1999-2009 at Brigham and Women's Hospital. The patient population consisted of 98 patients with no SHD diagnosed with idiopathic sustained VT, 358 patients with ICM and 239 patients with NICM.

All patients underwent echocardiography and/or magnetic resonance imaging to screen for the presence of SHD and to define ventricular function. The distinction

between ICM and NICM was based primarily on the presence of relevant coronary artery disease confirmed with a coronary angiography. NICM was identified as an absence of relevant coronary artery disease and defined according to the criteria of the European Society of Cardiology Working Group for Myocardial and Pericardial Diseases.[7] Patients with premature ventricular contractions or ventricular fibrillation (VF) induced by premature ventricular contractions as the procedural indication were excluded. All patients gave written informed consent for the procedure and the study analysis was performed according to protocols approved by the Brigham and Women's Hospital Human Subject Protection Committee.

Mapping and Ablation

Our approach to percutaneous endocardial and epicardial mapping and ablation has been described previously.[8] Briefly, programmed ventricular stimulation was performed with ≤3 extrastimuli after a drive train of 600 milliseconds [ms] and 400 ms from 2 right ventricular (RV) sites, and repeated from at least one left ventricular (LV) site if VT was non-inducible from RV stimulation. Isoprenaline or epinephrine was used upon the discretion of the operator. This protocol was repeated after ablation.

The morphologies of the induced VTs were compared to the spontaneously occurring VT(s) prior to ablation. Sustained monomorphic VT was defined as continuous VT for ≥30 seconds or one that required an intervention for termination (cardioversion, pacing or ablation).[9]

We defined "spontaneous VT" as any inducible VT with an identical 12-lead EKG morphology and rate (within 20 ms) to a VT that the patient presented with prior to

ablation. If 12-lead EKGs of the presenting VT were not available prior to ablation, the rate cut off and intracardiac electrogram (EGM) characteristics from the implantable cardioverter defibrillator (ICD) were used. "Undocumented VTs" were defined as inducible VTs that had a different cycle length (>20 ms difference), 12-lead EKG morphology or ICD-derived electrogram (EGM) characteristics compared to the VT that the patient had presented with prior to ablation.[9]

For VT associated with SHD, substrate mapping was performed with particular focus on pace-mapping in areas of low voltage (typically <1.5 millivolt [mV] bipolar electrograms) scar region facilitated by an irrigated catheter, and the CARTO electroanatomic mapping system (Biosense Webster, Diamond Bar, CA, USA). Areas of low voltage (<1.5 mV), dense scar (≤0.5mV) and electrically unexcitable scar were identified. Late potentials in the scar were tagged. Pace mapping was performed; areas of long stimulus to QRS (S-QRS) delays (>40 ms) and where pace mapping matched QRS morphology of an induced VT were tagged. If hemodynamically tolerated, VT was re-induced and activation/entrainment mapping performed. If not tolerated, it was terminated with radiofrequency ablation (RFA), burst pacing or cardioversion and substrate mapping performed. Ablation targeted presumptive channels, exits within the low-voltage area including regions of long S-QRS delays.[10] RFA was delivered with an irrigated catheter (ThermoCool or ThermoCool SF; Biosense Webster) at a power of 25 to 50 Watts targeting an impedance drop of 10 to 20 ohms. Applications were repeated at target areas until they were rendered electrically unexcitable with unipolar pacing at 10 milliamps at 2-ms pulse width.[10] Epicardial mapping was performed using the percutaneous approach if VT was suspected to be of epicardial origin, or if endocardial

ablation failed to terminate VT.[11] Coronary angiography was performed before epicardial ablation to avoid coronary injury; high output pacing was also performed to avoid ablation in close proximity to the phrenic nerve.

Intramural arrhythmia origin was inferred using published criteria as described in Supplemental Methods. Adjunctive non-RFA ablative methods such as transcoronary ethanol ablation (TCEA) or surgical cryoablation were performed when attempts at endocardial and/or epicardial mapping (where relevant), in addition to anti-arrhythmic (AAD) drugs failed to control VT. TCEA and surgical cryoablation was performed using techniques reported previously.[8]

The approach to the ablation of idiopathic VT relied on a combination on assessment of putative origin based on 12 lead EKG morphology, activation mapping during VT, assessment of pre-potentials and entrainment mapping (if possible) for fascicular VT and/or pace mapping when the VT was not reliably sustained or hemodynamically tolerated (for papillary muscle, LV summit or RV outflow tract VTs). Voltage and entrainment mapping were performed to exclude scar-mediated re-entry.

Outcomes

Acute procedural outcomes were reported as:

(a) complete success (defined as non-inducibility of any VT, either "spontaneous" and "undocumented");

(b) partial success (defined as abolishment of at least one "spontaneous" VT, but other "spontaneous" or "undocumented" VTs remained inducible);

(c) failure (persistent inducibility of "spontaneous" VT).

In follow up, outcomes reported were:

(a) VA-free survival: defined as any VT or VF that required treatment with AADs, internal or external cardioversion or anti-tachycardia pacing;

(b) survival free of cardiac transplantation;

(c) overall survival;

Outcomes were reported after the final procedure (multi-procedure outcomes, where relevant). The definition of major complications is detailed in Supplemental Methods.

Follow-Up

Follow up was defined from the time of the final ablation procedure to the time of death or last clinical follow up. Follow-up included review of records of all hospital and outpatient clinic visits and discussion with referring cardiologists and primary care physicians. The National Social Security Death Index was searched for mortality information. The approach to AAD management and defibrillator programming is detailed in Supplemental Methods.

Statistical Analysis

The Statistical Package for the Social Sciences for Windows (IBM SPSS, release 23, Armonk, NY, USA) was used for analysis. Continuous variables were expressed as mean ± standard deviation if normally distributed; median and interquartile range 25% to 75% (Q25–Q75) or full ranges were used if the data were clearly skewed. Where normal distribution was not present, log transformation of the raw values was performed to meet

the assumption of homogeneity of variance. Where applicable, paired sample t test was performed using the raw values (if normally distributed) or log-transformed values (if not normally distributed). Acute procedural success and complications were compared as categorical variables using the Fisher's Exact test. Overall survival, survival free of VA and transplant-free survival were estimated using the Kaplan–Meier procedure. Cox-proportional Hazard models were created to determine predictors of VA recurrence and all cause mortality. Models predicting mortality used recurrence as a time-dependent co-variable. Hazard ratios (HR) and 95% confidence intervals (CI) were used to express risk of VA recurrence and mortality. A two-tailed *P* value <0.05 was considered statistically significant.

Results

Baseline demographics

Relevant baseline characteristics are shown in Table 1. ICM patients were older, were more likely to be male, had greater left ventricular dysfunction, failed more anti-arrhythmic drugs prior to referral for catheter ablation, and had more refractory VT despite amiodarone compared to patients with no SHD and NICM (Table 1).

Procedural characteristics

More patients with ICM had a history of VT storm or incessant VT, compared with patients with NICM or no SHD (Table 2). ICM patients had a greater number of inducible VTs and longer ablation times compared to patients with no SHD or NICM.

Patients with NICM underwent a greater number of procedures for VT control than patients with ICM and those with no SHD.

Epicardial ablation was more frequently performed in the NICM patients compared to patients with no SHD or ICM. Adjunctive non-RFA ablation with TCEA or surgical cryoablation for VT refractory to anti-arrhythmic drugs and percutaneous ablation was performed with equal frequency in ICM and NICM patients; none of the SHD patients required an adjunctive non-RFA ablation (Table 2). Three patients had pre-existing mechanical LV assist devices but mechanical hemodynamic support was not used for ablation in any other patients.

Acute ablation outcomes

Acute complete success was achieved in 79% of no SHD, 60% of ICM and 56% of NICM patients (P<0.001 no SHD vs. others, P=0.4 ICM vs. NICM; Table 2). Partial success and/or failure were least common in patients with no SHD patients, but they were similar in the patients with ICM vs. NICM (Table 2).

Major complications were numerically lower in patients with no SHD (3.7%) compared with NICM patients (6.7%) and ICM patients (8.3%) but these differences were not statistically significant (Table 2, Supplemental Table 1).

Ventricular arrhythmia recurrences in follow up

Median follow up from the last ablation procedure was 6 years (Q25-Q75: 3-9 years). VA-free survival at median follow up in patients with no SHD was greater than ICM and NICM patients (77±5%, 54±4% and 38±4%, respectively; Figure 1). Early VA

recurrence, within 7 days of the procedure, occurred in 41% of SHD, 39% of NICM and 32% of ICM patients, respectively (P=0.5).

Factors associated with VA recurrence on multivariable analysis were LV ejection fraction (LVEF), presence of SHD (compared to no SHD), number of anti-arrhythmic drug failures, acute complete success at the end of the procedure, and epicardial ablation (Table 3; Supplemental Table 2). After adjusting for these factors, risk of VA recurrence was significantly lower in ICM vs. NICM patients (HR 0.7, 95% CI 0.6-0.9, P=0.02).

Mortality and Transplantation

Survival at median follow up in patients with no SHD was greater than NICM and ICM patients (100%, 74±3% and 48±3%, respectively; Figure 2). Survival free of cardiac transplant at median follow up in patients with no SHD was greater than ICM and NICM patients (100%, 96% and 89±2%, respectively; Figure 3).

Predictors of mortality

Factors associated with all cause mortality on multivariable analysis were age, LV ejection fraction, presence of SHD (versus no SHD), acute complete success, need for adjunctive non-RFA ablation methods, occurrence of a major complication and VA recurrence during follow up (Table 3; Supplemental Table 3). After adjusting for these factors, there was no significant difference in all cause mortality between the NICM vs. ICM patients (HR 1.1, 95% CI 0.8-1.5, P=0.5) even when VA recurrence was excluded from the model (no change in HR or 95% CI).

Factors associated with all cause mortality on multivariable analysis were different amongst patients with ICM versus NICM. In ICM patients alone, age, LVEF, acute complete success and VA recurrence during follow up were associated with all cause mortality on multivariable analysis (Supplemental Table 4). The same factors were also associated with all cause mortality in NICM patients, however the occurrence of a major complication were also associated whilst acute complete success was no longer associated with all cause mortality (Supplemental Table 5).

Discussion

This study catalogues the acute procedural and long-term outcomes of a large cohort of 695 patients followed for a median of 6 years and conveys a number of important findings:

1. The excellent prognosis in terms of survival free of death or transplant (100%) suggests that VT in patients without SHD is very rarely an initial presentation of a myopathic process;
2. Mortality is highest in ICM patients, such that half have died by 6 years after VT ablation;
3. VA recurrence is highest in NICM patients (three-quarters of patients have experienced at least one VA recurrence by 6 years after ablation); rates of cardiac transplantation are also highest in this population (11%). Whilst mortality is lower than ICM, it remains substantial in that 25% have died by 6 years after ablation;

4. Factors such as LVEF, presence of NICM, number of failed AADs, acute non-inducibility of any VT at the end of the procedure and need for epicardial ablation were independently associated with VA recurrence;
5. Age, LVEF, non-inducibility of any VT at the end of the procedure, need for adjunctive non-RFA treatment methods, occurrence of a major procedural complication and VA recurrence were independently associated with all cause mortality.

Prior studies

Prior prospective studies (including randomized trials) reporting outcomes of catheter ablation of sustained monomorphic VT have had a short duration of follow up, ranging from 6-24 months.[5, 12-14] As such, data on long term outcomes following VT ablation is limited, extending to 4 years in a retrospective study in patients with non-ischemic cardiomyopathy[15], 5 years in a retrospective study on arrhythmogenic right ventricular dysplasia,[3] and up to 3 years in a recent post-approval Multicenter Thermocool Ventricular Tachycardia Ablation Trial in patients with ICM.[2]

Whilst fundamental differences in VT substrate in the post-infarction versus non-ischemic cardiomyopathy has been appreciated,[4, 16] only a few studies have compared the long-term outcomes between these patients and none have been sufficiently powered to, nor detected, any differences in endpoints of mortality and transplantation.[5, 6, 16] Although prior studies have examined the predictive value of acute non-inducibility of VT at the end of the procedure for future recurrence of VA and mortality,[17-19] and of VA recurrence itself on mortality,[20] these studies have either been limited to a post-infarction setting,[17, 18]

or have analyzed a mixture of patients with both forms of heart disease.[20] Hence, the inter-relationship between clinical and acute procedural outcomes, in addition to VA recurrence and its influence on long-term mortality amongst specific disease substrates of ICM and NICM remains incompletely studied.

In this study, we provide detailed information on VA recurrence, transplantation and mortality by following one of the largest reported groups of patients with SHD for a median of 6 years. The study allows critical appraisal of long-term VT ablation outcomes, thus facilitating patient selection and providing information pertaining to the prognostic significance of intra-procedural parameters (e.g. need for adjunctive non-RFA modalities) and post-procedural endpoints (e.g. non-inducibility of any VT, major complications). An advantage of a large single center report is the near uniform VT ablation protocol. In contrast, prior multi-center reports encompass heterogeneous ablation approaches.[18, 20]

The overall survival of ICM patients was worse than NICM patients even though there were more VA recurrences in the NICM patients. The worse mortality is likely related to worse LVEF and older age in ICM compared to NICM patients. The longer survival of NICM may also allow more time for recurrent VAs. It is important to recognize that these differences may have a major impact on the different outcomes in ICM vs. NICM patients that may not be completely accounted for in statistical models.

Our SHD patients had recurrent arrhythmias and severely depressed ventricular function, characteristic of advanced heart disease. The population had a lower mean LVEF, a higher proportion of patients with a very low LVEF of ≤30% and more patients who had failed amiodarone prior to VT ablation compared to the ablation arms of the

SMASH-VT[13] or the V-TACH studies.[12] Thus our population represents a higher risk cohort with likely more advanced heart disease and later referral for VT ablation. As has been suggested by others,[21, 22] earlier use of catheter ablation may have improved outcomes in our cohort and warrants further study. The present study also has a long recruitment period during which time procedural techniques evolved with improvements in mapping and ablation technologies and strategies that will hopefully translate to better outcomes.

Limitations

This is a retrospective report from a high volume center for VT ablation. It is possible other confounding variables not collected may have added to the VA recurrence or mortality risk in the study. Furthermore, referral biases are present such that results may be skewed to the sickest cohort of ICM and NICM patients that may limit generalizability. However this is one of the largest series reporting outcomes with the longest duration of follow up of any prior study.

Conclusions

Long term follow up after VT ablation demonstrates the benign prognosis in patients without SHD, suggesting that VT is this population is very rarely an initial presentation of a myopathic process. Despite the advanced heart disease typically present in patients with VT due to structural heart disease, survival beyond 5 years is common. Patients with ICM face the highest mortality risk such that more than half died by 6 years post ablation. In contrast, NICM patients face the highest risk of VA recurrence such that three-quarters

experienced a recurrence, one tenth were transplanted and one-quarter died by 6 years following VT ablation. The higher mortality risk in ICM compared with NICM patients was explained by factors such as age, LVEF, acute procedural success and complications, challenging substrates requiring adjunctive non-RFA ablation modalities and recurrence of VA in follow up.

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Tables

Table 1: Baseline data

	No SHD (n=98 patients)	NICM (n=239 patients)	ICM (n=358 patients)	P value no SHD vs. others	P value ICM vs. NICM
Age, mean ± SD, years	47±15	52±14	67±10	<0.001	<0.001
Male gender, %	49	79	86	<0.001	0.02
LVEF, mean ± SD, %	61±6	40±17	28±12	<0.001	<0.001
LVEF ≤ 30%	0	68	40	<0.001	<0.001
Number of failed anti-arrhythmic drugs, mean ± SD	1.6±1.3	2.1±1.3	2.6±1.4	<0.001	<0.001
Failed amiodarone prior to ablation, %	17	65	81	<0.001	<0.001
Implanted defibrillator, %	0	77	90	<0.001	<0.001
Cardiac re-synchronization device, %	0	12	20	<0.001	0.01
NYHA class ≥ II	0	58	56	<0.001	0.8
Subtype of NICM heart disease, n, % of all NICM patients					
Idiopathic dilated		132 (55)			
Arrhythmogenic right ventricular dysplasia		39 (16)			
Sarcoidosis		12 (5)			
Valvular		30 (13)			
Congenital		19 (8)			
Other[a]		7 (3.4)			

[a]Hypertrophic cardiomyopathy 6, restrictive cardiomyopathy 1

Abbreviations: ICM-ischemic cardiomyopathy, LVEF-left ventricular ejection fraction; NICM-non-ischemic cardiomyopathy, NYHA- New York Heart Association Class; Q25-Q75- interquartile range 25%-75%, SD-standard deviation, SHD-structural heart disease

Table 2: Procedural characteristics

	No SHD (n=98 patients)	NICM (n=239 patients)	ICM (n=358 patients)	P value no SHD vs. NICM/vs. ICM	P value ICM vs. NICM
Sustained VT as indication for procedure	98 (100)	239 (100)	358 (100)	-	-
Total number of VT ablation procedures performed, (mean ± SD of procedures performed/patient)	109 (1.1± 0.4)	341 (1.4± 0.7)	470 (1.3± 0.6)	<0.001/0.9	<0.001
Number of patients undergoing:	88	161	267	-	-
1 procedure	9	55	76		
2 procedures	1	23	15		
≥ 3 procedures					
Interval between first and last procedure, years, mean ± SD (median; IQR 25-75%)	1.5 ± 2.4 (0.5; 0.01-2.2)	1.2 ± 1.8 (0.4; 0.02-1.8)	0.6 ± 1.2 (0.07; 0.01-0.7)	0.8/0.1	0.003
Procedural indication of VT storm, n/total number of procedures (%)	13/109 (12)	84/340 (25)	145/470 (31)	0.007/<0.001	0.06
Number of inducible VTs per procedure, mean ± SD	1.1±0.5	2.4±1.6	2.8±1.7	<0.001 (both)	<0.001
RF ablation time, mean ± SD, minutes	11.8±9.6	24.7±21.5	33.3±22.4	<0.001 (both)	<0.001
Fluoroscopy time, mean ± SD, minutes	31.3±20	43±21.6	45.1±30.2	<0.001 (both)	0.8
Origin of idiopathic VT, n/number of patients (%)	53 (54)				
RV outflow tract	6 (6)				
LV outflow tract	4 (4)				
LV summit	1 (1)				
Papillary muscle	3 (3)				
Aortic-mitral continuity or mitral annular origin	3 (3)				
Right parahisian	4 (4)				
Epicardial[a]	1 (1)				
LV lateral	20 (20)				
RV free wall					
Other focal LV					

VT (including fascicular or Purkinje-related)					
Epicardial ablation required during at least one procedure, n/number of patients (%)	3/98 (3)	71/239 (30)	30/358 (8)	<0.001/0.08	<0.001
Non-RFA requirement (transcoronary ethanol or surgical cryoablation), n/number of procedures (%)	0/109 (0)	21/341 (6.2)	21/470 (4.5)	0.003/0.02	0.4
Acute procedural outcome after final procedure, %	79	56	60	<0.001/0.001	0.4
Complete success	3	19	20		
Partial success	12	13	9		
Failure	6	12	11		
Not tested or non-inducible at beginning					
Major complications, n/number of procedures (%)	4/109 (3.7)	23/341 (6.7)	39/470 (8.3)	0.4/0.1	0.4

[a]epicardial lateral wall LV 2, epicardial RVOT 1

Abbreviations (in addition to above): LV-left ventricle; ms-milliseconds, RV-right ventricle; VT-ventricular tachycardia.

Table 3: Factors associated with VA recurrence and all cause mortality

Variable	Multivariable HR for VA recurrence (95% CI)	P value	Multivariable HR for all cause mortality (95% CI)	P value
Age	-		1.05 (1.04-1.06)	<0.001
Male gender	-		-	-
LVEF (each 1% increase)	0.99 (0.98-0.99)	0.01	0.96 (0.95-0.97)	<0.001
Type of SHD				
ICM (vs. no SHD)[a]	1.7 (0.9-2.9)	0.09	15.5 (3.8-63.2)	<0.001
NICM (vs. no SHD)	2.3 (1.3-3.9)	0.003	13.8 (3.4-56.8)	<0.001
Number of failed anti-arrhythmic drugs	1.1 (1.003-1.22)	<0.001	-	-
History of VT storm	-	-	-	-
Acute complete success	0.65 (0.52-0.82)	<0.001	0.7 (0.58-0.94)	0.01
Epicardial ablation	1.5 (1.1-2)	0.01	-	
Need for adjunctive non-RFA ablation	-	-	1.6 (1.04-2.4)	0.03
Major complication	-	-	1.6 (1.1-2.3)	0.03
VA Recurrence[b]	Not entered	-	1.8 (1.4-2.4)	<0.001

[a]HR for VA recurrence comparing ICM vs. NICM was 0.7 (95% CI 0.6-0.9, P=0.02); HR for all cause mortality comparing NICM vs. ICM: HR 1.1 (95% CI 0.8-1.5), P=0.5
[b]added as a time-dependent co-variate

Abbreviations (in addition to above): RFA-radiofrequency ablation, VA-ventricular arrhythmia.

Figure Legends

Figure 1: Survival free of recurrent ventricular arrhythmia in the no structural heart disease (no SHD), ischemic cardiomyopathy (ICM) and non-ischemic cardiomyoptahy groups (NICM).

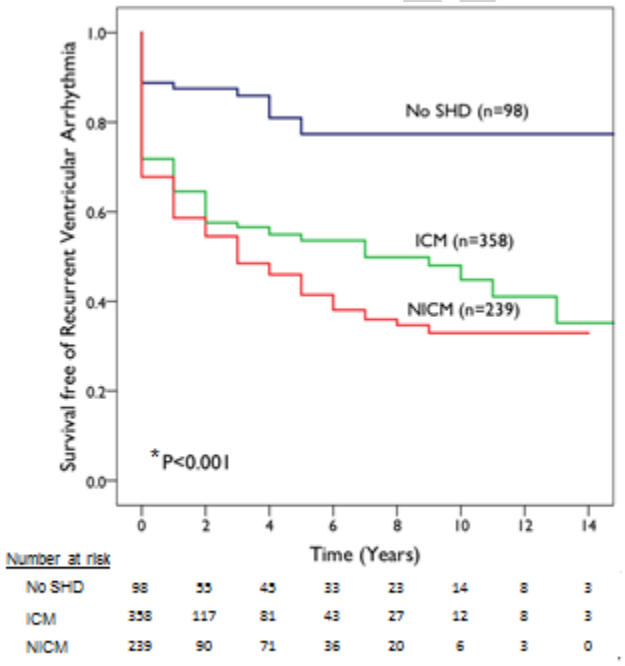
*No SHD vs. ICM P <0.001; No SHD vs. NICM P<0.001; ICM vs. NICM P=0.03

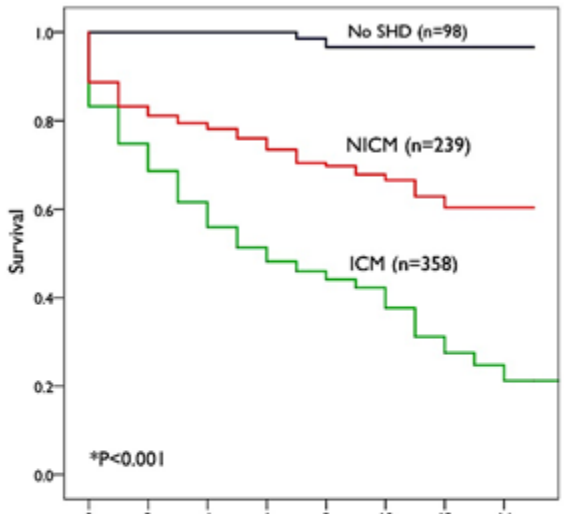
Figure 2: Overall survival in the no SHD, ICM and NICM groups.

*P<0.001 between all 3 groups

Figure 3: Survival free of cardiac transplant in the no SHD, ICM and NICM groups.

*No SHD vs. ICM P =0.08; ICM vs. NICM P=0.002; no SHD vs. NICM P=0.002.





Number at risk								
No SHD	98	97	95	70	42	23	15	6
NICM	239	192	180	121	73	36	16	3
ICM	358	244	195	131	71	29	10	5